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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/423,622	02/08/2000	HANS WERNER MULLER	P64029USO	6964

136 7590 02/24/2003

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EXAMINER	
BUNNER, BRIDGET E	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 02/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/423,622	MULLER ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this c mmunication appears on the c ver sheet with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 November 2002 (Paper No. 22)* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36-47* is/are pending in the application.

4a) Of the above claim(s) *30-35 and 39-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36-38 and 42-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *36-47* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Prosecution Application

The Request for Continued Prosecution Application (CPA) filed on 07 May 2002 (Paper No. 18) under 37 CFR 1.114 based on parent Application No. 09/423,622 is acceptable and a CPA has been established. An action on the CPA follows.

Status of Application, Amendments and/or Claims

The amendments of 18 November 2002 (Paper No. 22) and 08 April 2002 (Paper No. 15) have been entered in full. Claims 18-29 and 35 are cancelled and claims 36-47 are added.

Claims 30-35 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claims 30-35 are directed to a non-elected group that was previously restricted in Paper No. 7 (08 August 2000).

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 30-35 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 39-41 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. The Examiner erroneously examined claims 22-24 (which correspond to claims 39-41) in the first Office Action of 08 November 2000 (Paper No. 9). Currently cancelled claims 22-24 should have been withdrawn as being drawn to a non-elected species. Applicant timely traversed the restriction (election) requirement in Paper No. 8 (21 September 2001).

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 36-38 and 42-47 are under consideration in the instant application.

Withdrawn Objections and/or Rejections

1. The objection to the specification as set forth at pg 3 of the previous Office Action (Paper No. 12, 07 May 2001) is *withdrawn* in view of the amended sentence of the specification (Paper No. 15, 08 April 2002).

2. The objection of claim 23 as set forth at pg 3-4 of the previous Office Action (Paper No. 12, 07 May 2001) is *withdrawn* in view of the cancelled claim (Paper No. 15, 08 April 2002). Please see New Claim Objections, below.

3. The rejection of claims 18, 23, and 25-29 under 35 U.S.C. § 112, second paragraph, as set forth at pg 5-6 of the previous Office Action (Paper No. 12, 07 May 2001) is *withdrawn* in view of the cancelled claims (Paper No. 15, 08 April 2002). Please see section below on 35 U.S.C. § 112, second paragraph.

4. The rejection of claims 18-20 under 35 U.S.C. § 102(b) as set forth at pg 6-7 of the previous Office Action (Paper No. 12, 07 May 2001) is *withdrawn* in view of the cancelled claims (Paper No. 15, 08 April 2002).

5. The rejection of claims 21-24 under 35 U.S.C. § 103(a) as set forth at pg 7-9 of the previous Office Action (Paper No. 12, 07 May 2001) is *withdrawn* in view of the cancelled claims (Paper No. 15, 08 April 2002).

New Claim Objections

6. Claims 37-38 are objected to because of the following informalities:

6a. Claims 37 and 38 recite a non-elected species.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, first paragraph

7. Claims 36-38 and 42-47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of enhancing axonal regeneration comprising locally administering an inhibitor substance that inhibits basal membrane formation of the lesioned postcommissural fornix to enhance axonal regeneration, and wherein the inhibitor substance is an anti-collagen IV antibody or α, α'-dipyridyl (DPY), does not reasonably provide enablement for a method for the improvement of the CNS after axonal regeneration or a method of enhancement of axonal regeneration comprising specific inhibition of basal membrane formation induced by a lesion of neuronal tissue comprising administering systemically or locally, to a body in need thereof, an inhibitor of basal membrane formation wherein the inhibitor substance is an inhibitor of the synthesis of basal membrane building elements, an inhibitor of the assembly of basal membrane building elements, or the inhibitor of the synthesis of basal membrane building elements and the inhibitor of the assembly of basal membrane building elements. The basis for this rejection is set forth in the rejection of claims 18-29, at pg 4-5 of the previous Office Action (Paper No. 12, 07 May 2001).

Applicant's arguments (pg 5, Paper No. 15, 08 April 2002) have been fully considered but are not found to be persuasive for the following reasons:

Applicant asserts that by amending claim 18 as claim 36, concerning the exchange of neuronal regeneration to axonal regeneration renders moot the rejection under 35 USC § 112, first paragraph. Applicant also contends that reciting "improvement of the CNS after axonal

regeneration" further overcomes the rejection. Applicant argues that the alternative generic claim 47 recites "enhancement of axonal regeneration" for which enablement exists according to the statement of rejection.

Applicant's arguments have been fully considered but are not found to be persuasive. The specification of the instant application teaches that lesion-induced basal membrane deposition can be reduced in the transected postcommissural fornix of the adult rat by local injection of anti-collagen IV antibodies or α, α' dipyridyl (DPY) (pg 6, ¶ 3; Figures 1-4). The specification also discloses that the elongation of fornix axons after anti-Coll IV or DPY treatment is studied (pg 8, ¶ 2). The specification teaches that sprouting fornix fibers in control animals cease growing at the proximal stump-lesion interface while large numbers of axons enter and traverse the lesion center after lesion+injection in animals receiving anti-Coll IV or DPY treatment (pg 8, ¶ 2). The specification teaches that the regenerating fornix fibers followed the original pathway, reinnervated the mammilary body target, were remyelinated and attained nearly normal conduction properties (pg 6, ¶ 3; pg 8, ¶ 2). However, the specification of the instant application does not teach any methods or working examples that indicate improvement of the central nervous system after axonal regeneration. The specification also does not teach administering all possible inhibitors of basal membrane formation, particularly all possible inhibitors of the synthesis of basal membrane building elements and all possible inhibitors of the assembly of basal membrane building elements. Undue experimentation would be required of the skilled artisan to test all possible inhibitors of basal membrane formation. Furthermore, the specification does not teach the region of the CNS, which encompasses the brain and spinal cord, that the claimed methods are applicable to. The specification also does not teach which cell

types the claimed methods are applicable to. Therefore, according to the broad claim language, the examiner assumed that the invention could be applied to both brain and spinal cord lesions. The specification does not provide any experiments or examples showing that the method of the invention can be successfully applied to spinal cord lesions. Although both CNS components, the brain and the spinal cord may respond differently to the same form of treatment and also may require different doses of the inhibitor substance. Furthermore, the specification of the instant application does not disclose administering the inhibitor substance intraventricularly, systemically, orally, or intravenously. Relevant literature reports that the goal of delivering drugs noninvasively has only achieved modest success, with poor applicability to proteins and peptides (pg 343, col 1-2; Pettit et al. Trends Biotechnol 16: 343-349, 1998). The problems posed by proteins and peptides is their large molecular size, electrical charge, relatively hydrophilic nature, and relative instability in environments of extreme pH or proteolytic activity (such as the stomach and intestine) (pg 343, col 2). Pettit et al. review several routes of protein administration and the limitations that have been encountered. For example, limited success has been achieved delivering proteins and peptides orally because of: 1) poor intrinsic permeability across intestinal epithelium, 2) susceptibility to enzymatic attack, 3) rapid post-absorptive clearance, and 4) chemical instability (pg 344-345). Additionally, proteins or peptides administered systemically must resist clearance via molecular filtration by the kidney and clearance by the reticuloendothelial system (pg 345, col 2). Although the pulmonary delivery route has generated the most encouraging data, the bioavailability of proteins (i.e. the amount of protein that crosses from the alveoli in to the pulmonary circulation) is dependent on the physical characteristics of the delivered protein and is not the same for proteins and peptides in general

(pg 343-344). Therefore, the state of the prior art establishes the unpredictability of delivering substances, such as proteins, to a subject.

Proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary to improve the CNS and to enhance axonal regeneration comprising inhibition of basal membrane formation induced by a lesion of neuronal tissue, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to inhibition of basal membrane formation of the spinal cord, the complex nature of the invention, the unpredictability of axon regeneration and of the effects of delivering the inhibitor substance intraventicularly, systemically, orally, or intravenously to a subject, and the breadth of the claims which fail to recite limitations on the region of the CNS affected and the type of neuronal cells that sprout axons, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112

8. Claims 36-38 and 42-47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. The term "improvement of the CNS" in claims 36-38 and 42-46 is a relative term which renders the claim indefinite. The term "improvement of the CNS" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It cannot

be determined if "improvement of the CNS" means for example, curing a disease, healing an injury, increasing cell number, etc.

10. Claims 36-38 and 42-47 are indefinite because the claims do not have a step that clearly relates back to the preamble. For example, there is no step indicating how cellular metabolism has to change in order to identify the test compound as an agonist or antagonist.

Allowable Subject Matter

11. An example of an allowable claim is recited below:

A method of enhancing axonal regeneration comprising locally administering an inhibitor substance that inhibits basal membrane formation of lesioned postcommissural fornix to enhance axonal regeneration, and wherein the inhibitor substance is an anti-collagen IV antibody or α, α'-dipyridyl (DPY).

Conclusion

No claims are allowable.

The art made of record and not relied upon is considered pertinent to applicant's disclosure:

Hermanns et al. Society for Neurosci Abs 26(1-2): 3236, 2000.

Joosten et al. J Neurosci Res 62: 686-691, 2000.

Stichel et al. Neurosci 93(1): 321-333, 1999

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:30-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 872-9305.

Elizabeth C. Kemmerer

BEB
Art Unit 1647
February 12, 2003